Targeted Temperature Management in Subarachnoid Haemorrhage

Keller, E

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Targeted Temperature Management in Subarachnoid Haemorrhage

Emanuela Keller, Neurocritical Care Unit, University Hospital Zurich, Switzerland

Patients with subarachnoid haemorrhage (SAH) can benefit from hypothermia but the mechanisms by which this occurs are poorly understood. The pathophysiology following SAH is complex. Cerebral blood flow (CBF) through the capillaries is affected by several factors including cerebral vasospasm (CVS) but also by CPP and resistance at the arteriolar and possibly venous levels. Alterations in the latter two factors may manifest as slowed circulation time and poor vessel filling as seen on angiography but these cannot be necessarily be correlated with CVS.[31] Following SAH, there is a strong inflammatory response that is induced by the breakdown of erythrocytes in the subarachnoid space. This reaction induces secondary ischaemia due to vasospasm but also contributes to the development of brain oedema. To prevent such oedema, early intervention in the inflammatory cascade is essential.[32]

The damaging effect of inflammatory cytokines was demonstrated in a study of 138 patients with SAH.[33] Unfavourable outcome (Glasgow Outcome Scale [GOS] 1–3) and delayed ischaemic neurological deficits (DINDs) were significantly associated with elevated blood IL6 levels during the early phase ($p=0.023$ and $p=0.026$, respectively). It was suggested that IL6 levels could be a useful parameter to monitor following SAH. A pilot study (n=15) reported that IL6, tumour necrosis factor α (TNF α) and IL1β increase in blood and cerebrospinal fluid in patients after SAH although IL6 was at 100-fold higher levels in CSF than blood.[34]

Hypothermia, with a target range of 33–34°C using combined therapy with endovascular cooling and barbiturate coma, markedly reduced both IL6 and IL1β ($p<0.001$ for both) indicating its efficacy in attenuating the inflammatory cascade.

The ratio between IL6 levels in the CSF and plasma, as a parameter for intrathecal synthesis, furthermore, was significantly lower in patients who received combined therapy compared with those who did not receive it ($p=0.014$).

Other work on adult rats indicates that hypothermia reduces vasospasm and decreases the reduction in cerebral blood flow and oxygenation following SAH but the greatest benefit is gained when the treatment is within hours after aneurysm rupture.[35]

Cooling the brain in SAH is likely to reduce metabolism, however, the optimal target temperature has not been determined. Some studies have shown that, while patients are cooled, uncoupling between CBF and $CMRO_2$ occurs to the extent that CBF exceeds the metabolic demand. This phenomenon is known as luxury perfusion.[36] This concept was supported by a small case series of patients with SAH and hypothermia (33–34°C) provided some preliminary evidence of hypothermia-induced luxury perfusion in which a larger decrease in $CMRO_2$ (54.3%) compared with CBF (35.7%) was observed.[37]

Fever is the most frequent symptom in SAH, occurring in approximately 75% of patients and is strongly associated with death or severe disability as outcomes.[38] In SAH, fever is more common than hyperglycaemia, hypertension, pneumonia and delirium. A meta-analysis of 24 studies in 2010 found that fever during acute hospitalisation for SAH was consistently linked with worsened outcome and increased mortality.[39] Antipyretic medications, surface cooling and intravascular cooling may reduce fevers but the benefits from these measures may be offset by negative consequences of shivering.[39] The potential negative consequences of fever reduction were also indicated by a study of 21 consecutive aneurysmal SAH patients who were given diclofenac.[40] This treatment effectively reduced body temperature but this led to 10% decrease in mean arterial pressure and CPP ($p<0.001$) and a 13% decrease in $PbtO_2$ and brain hypoxia in 38% of patients. This suggested that fever reduction in SAH using diclofenac is not always beneficial and should be exercised with care.

Intravascular cooling can also be associated with thromboembolic events. In a study of 122 patients, among those with central venous lines (n=79) 5% had deep vein thromboses (DVT) or pulmonary embolism (PE).[41] Among those with endovascular cooling catheters, however, (n=43) 37% had DVT or PE (52% in those treated for fever and 23% for those treated with hypothermia). In the treatment of fever in SAH, therefore, there is a need for prospective controlled trials that investigate the side effects; they should possibly use surrogate markers to determine outcomes including such as cerebral haemodynamics and metabolism, inflammatory response and secondary brain injuries.

Hypothermia treatment is not always associated with favourable outcomes. This was shown in a study of 441 consecutive patients with SAH in which 100 patients developed raised ICP or symptomatic CVS that was refractory to treatment.[42] Patients were treated with TTM using ice, water blankets or intravascular cooling (33–34^{o}C) which was maintained until intracranial pressure normalized, CVS resolved, or there were severe side effects. Among these patients, only 25% with raised ICP, 57.1% with CVS and 26.5% with ICP/ISV showed favourable outcomes (Glasgow Outcome Scale 4 or 5). It was concluded that prolonged systemic hypothermia should be considered a last resort option in SAH with raised ICP or CVS that is resistant to treatment. A more recent pilot study, however, showed more positive findings for therapeutic hypothermia (TTM) in SAH.[43] A group of 12 patients with SAH who received early TTM (within 48 h) showed reduced delayed cerebral ischaemia (DCI) and microvascular spasm compared with 24 matched patients from an SAH database. TTM significantly decreased macrovascular spasm and peak spastic ($p < 0.05$). The frequency of DCI was reduced from 87.5% in non-TTM to 50% in TTM-treated patients, creating a preventive risk ratio of 0.33 ($p=0.036$). Favourable functional outcomes were significantly more frequent in TTM-treated patients (66.7% vs. 33.3% of non-TH-treated patients, $p=0.06$ – see ***Figure 4***).

- **Animal studies have improved the understanding of SAH pathophysiology**
- **Intravascular catheters are associated with increased risk of thrombosis**
- **Larger retrospective case series show that TTM is a last resort treatment of intracranial hypertension and vasospasm**
- **Findings in a recent prospective pilot study showed that TTM treatment can be beneficial in high-grade SAH patients**
- **A prospective randomized study in high-grade patients with prophylactic TTM is needed and should include a few centres with a very strictly controlled treatment protocol**

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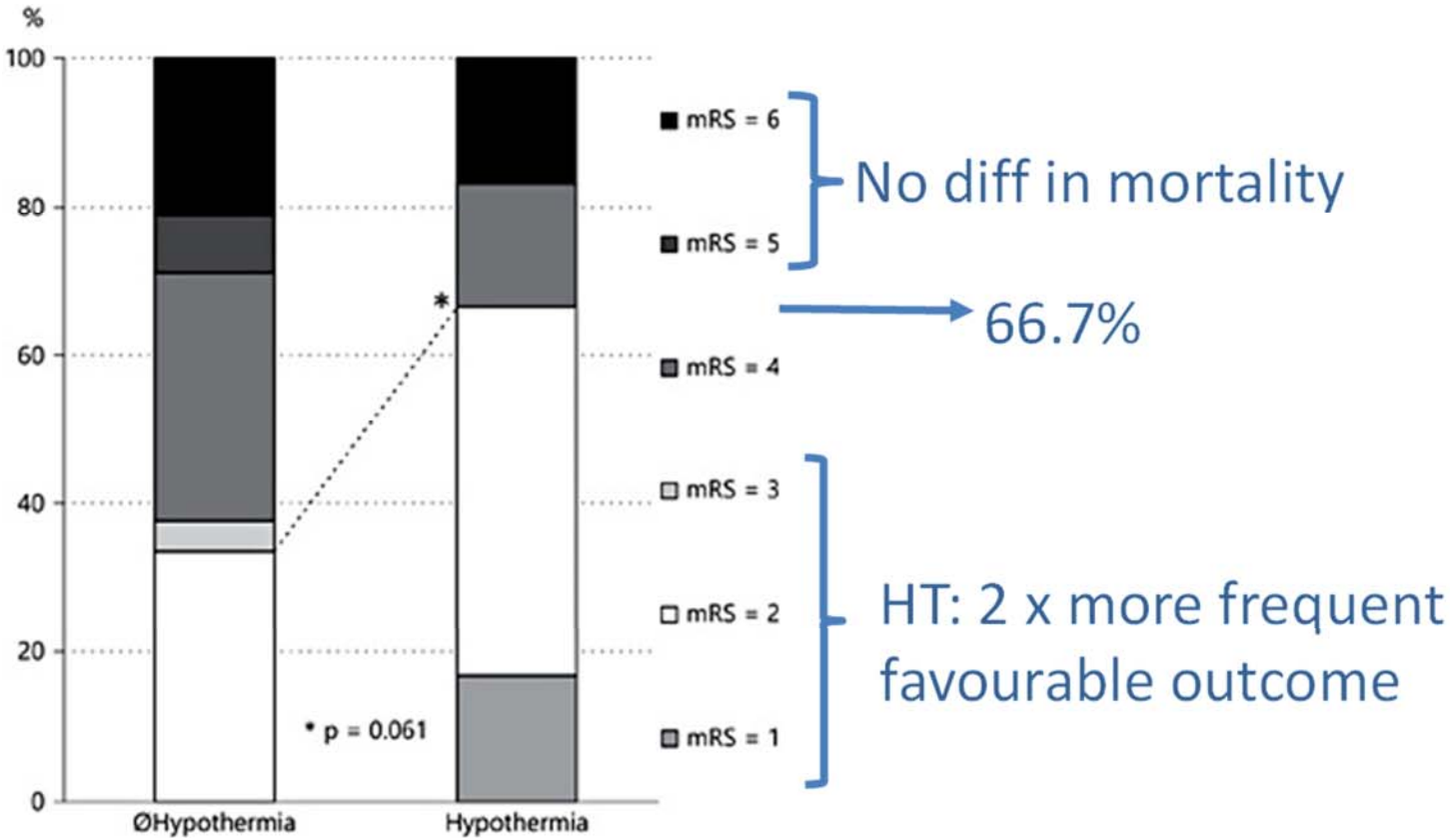
Figure 4

Effect of hypothermia treatment versus no hypothermia treatment on outcomes in a series of patients with subarachnoid haemorrhage



Source: Karamatsu et al., 2015[43]